in regulation of cell division, membrane stability and matrix-elasticity sensing during human hematopoietic stem cell (HSC) differentiation. Myosin is required for the survival of proliferating myeloid progenitors, while long-term primitive HSCs are resistant to myosin inhibition. In contrast, inhibition of cellular contractility facilitates megakaryocyte (MK) maturation by polyploidization and fragmentation into functional platelets in vivo (median fragmentation threshold at ~1mN/m in vitro). In addition, differences in local tissue stiffness - such as exists between cortical bone and marrow - likely contribute to HSC differentiation because in vitro adhesion to stiff (34kPa) collagenous matrices tends to inhibit MK maturation whenever myosin is inhibited, while soft (0.3kPa) matrices with lower amount of collagens tend to facilitate this process. Quantitative mass spectrometry and confocal microscopy indicate both global remodeling of cytoskeletal proteomes and extensive lamin network formation during MK maturation, providing MKs in bone marrow with an ideal structure to shed platelets into permeating capillaries. Together, these data show that cell relaxation and soft matrices maintain primitiveness of HSCs and drive MK differentiation, whereas the opposite physical cues support HSC differentiation into myeloid progenitors.

2395-Pos Board B381
Stochastic Simulation Study of the Role of Capping and Anti-Capping Proteins in Regulating Actin Network Growth
Longhua Hu, Garegin A. Papoian.
Actin-based cell motility is essential to many biological processes. We build simplified computational model and perform stochastic simulation to study the growth of lamellipodia-like branched filamentous network. Here we investigate how capping proteins and anti-capping proteins affect the speed of protrusion and the nucleation of filaments in the model system. Phase diagram showing the regimes of motility enhancement and motility inhibition is presented. Furthermore, we discuss filament length distribution and its implication in the formation of filopodia from lamellipodial network.

2396-Pos Board B382
Discrete 3-Dimensional Modeling of Tumor Cell Growth and Migration
Parag Katira, Muhammad H. Zaman, Roger T. Bonnecaze.
A variety of genetic factors causing up-regulation or down-regulation of key enzymes have been attributed to affect the malignancy of tumors. Yet, the ability to predict the aggressiveness of tumors in terms of their growth rate and metastatic potential is fairly limited. We hypothesize that the genetic and enzymatic factors only indirectly influence tumor growth and metastasis and that these processes are primarily physical in nature. This is based on observations that the physical state of a cell plays a major role in determining its fate - division, survival, migration and apoptosis. The physical state of a cell (shape and size) is a direct function of the physical properties of the cell such as the osmotic pressure, the cytoskeletal stiffness and the strength of inter-cellular and cell-matrix bonding. We have developed a computational model describing the physical state of discrete cells in a 3-dimensional tissue environment as a function of the physical properties of cells. Using this model and a cell shape dependent cell death and division rate we recreate the conditions for cell turnover and tissue homeostasis. We then probe the influence of changes in a cell's physical properties on its division rate and apoptosis. The changes in physical properties that cause an uncontrolled growth and division of cells can be identified. Cells with these characteristics correspond in nature to tumor cells. Computer simulations based on this model provide information on the growth rate of particular tumors with cells displaying specific physical properties as well as the shape evolution of these tumors. The identification of changes in physical properties of a cell that drive tumor cell growth and division helps isolate key genetic and enzymatic factors that influence these properties and the mechanism by which they drive tumor progression.

2397-Pos Board B383
Loss of an Actin Crosslinker Uncouples Cell Spreading from Cell Stiffening on Gels with a Gradient of Stiffness
Qi Wen, Fitzroy J. Byfield, Kerstin Nordstrom, Paulo E. Arratia, R. Tyler Miller, Paul A. Janmey.
We show the essential function of an actin crosslinker, filamin A, in cell responses to mechanical stimuli by measuring the stiffness, spreading area of A7 and M2 cells cultured on substrates with stiffness gradients created by microfluidics. M2 melanoma cells, null for filamin A, do not alter their adherent area in response to increased substrate stiffness when they link to the substrate only through collagen receptors, but change adherent area normally when bound through fibronectin receptors. In contrast, filamin A-replete A7 cells change adherent area on both substrates and respond more strongly to collagen I-coated gels than to fibronectin-coated gels. A7 cells alter their stiffness, as measured by atomic force microscopy, to match the elastic modulus of the substrate immediately adjacent to them on the gradient. M2 cells, in contrast, maintain a constant stiffness on all substrates that is as low as that of A7 cells on the softest gels achievable (1000 Pa). Comparing the responses of these cell types to different adhesive substrates, we found that cell spreading and stiffening can be uncoupled.

2398-Pos Board B384
PDMS Thin Films Used to Image Stretch Induced Changes in Axonal Cytoskeletal Dynamics
Joshua Chetta, Sameer Shah.
We have previously shown that an externally applied stretch is not uniformly distributed along the length of the axons of cultured rat sensory neurons. In order to further identify the role of individual cytoskeletal components in this heterogeneous strain distribution, the introduction of cytoskeleton-modifying drugs is desired. In our previous work, it was necessary to invert cells in order to image the axons during loading. This inversion restricted access to the cells and precluded the exposure of cell to drugs. To accommodate drug delivery we have developed a new cell stretching protocol utilizing poly-dimethyl-siloxane (PDMS) thin films as a culture substrate which allows cells to be imaged upright and provides access for drug delivery. PDMS films were spin cast onto custom fabricated polycarbonate discs. Rat sensory neurons were cultured on PDMS thin films and the dynamic positions of cytoskeletal markers were monitored before stretch and for 20 minutes following a 10% applied stretch in the presence of nocodazole to depolymerize microtubules or latrunculin to depolymerize actin. The results were analyzed using kymographs created by a custom designed matlab program to elucidate the role of individual cytoskeletal components to the distribution of strain in stretched axons.

2399-Pos Board B385
The Role of Stretching in Slow Axonal Transport
Matthew R. O'Toole, Kyle E. Miller.
Axonal stretching is linked to rapid rates of axonal elongation. Yet the impact of stretching on elongation and slow axonal transport is unclear. Here we develop a mathematical model of slow axonal transport that incorporates the rate of axonal elongation, protein half-life, protein density, adhesion strength, and axonal viscosity to quantify the effects of axonal stretching. Under conditions where the axon (or nerve) is free of a substrate and lengthens at rapid rates ($>$ 4 mm day), we find stretching can account for almost 50% of total anterograde axonal transport. These results suggest it is possible to accelerate elongation and transport simultaneously by increasing either an axon''s susceptibility to stretching or the forces that induce stretching. This work is the first to incorporate the effects of stretching in a model of slow axonal transport. It has relevance to understanding neurite outgrowth during development, peripheral nerve regeneration after trauma, and for the development of treatments for spinal cord injury.

2400-Pos Board B386
Mechanisms of Cytokinetic Ring Constriction in Fission Yeast
Matthew R. Stachowiak, Caroline Laplante, Boris Guirao, Patricia Garcia, Thomas D. Pollard, Ben O'Shaughnessy.
Cytokinesis, the physical process of cell division, is accomplished by constriction of an actomyosin ring in eukaryotic cells. Here we combined mathematical modeling and experiment to study ring constriction in fission yeast, a model organism as many ring components have been identified and their concentrations measured. The ring model implemented random actomyosin organization, consistent with experiment, and actin turnover mediated by formin and cofilin severing proteins with parameters determined by experimental measurements of turnover rates. An obstacle to quantitative modeling is that ring constriction is tightly coupled to the poorly understood process of septation, the deposition of new cell wall in the wake of the constricting ring. Thus we studied yeast protoplasts whose cell walls have been enzymatically digested. We found that protoplasts contain ring precursor nodes similar to normal cells and assemble functional contractile rings that constrict without septation by sliding along the plasma membrane. Thus we could directly compare model predicted ring constriction profiles to experiment. Using this approach we found constriction is driven by tensions ~14-25 pN, far less than those measured in animal cells, and the strength of ring-membrane anchoring during constriction is ~9 times the value of all the precursor nodes combined. The model showed ring tension requires actin anchoring and is maximized when the barbed ends are anchored. The tension magnitude is determined by a measurable statistical characteristic of the actomyosin spatial organization which quantifies actin-myosin correlations and describes the degree to which the organization possesses the optimal tension-generating sarcomeric architecture of muscle. Consistent with experiment, suppression of the actin polymerization rate increased the ring constriction time because actin filaments are shorter and hence actin-myosin coupling and tension are diminished. Thus, the model articulates a mechanistic relationship between organization, turnover kinetics and tension.